UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,905	08/08/2001	Ronald R. Breaker	OCR-794B.US	5301

7590 01/02/2003

Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C
One Financial Center
Boston, MA 02111

EXAMINER
SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n N .	Applicant(s)	
	09/830,905	BREAKER ET AL.	
	Examiner	Art Unit	
	Mary M. Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *8 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 9-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 August 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election of Group I, claims 1-7 and 9-20, in Paper No. 10, filed 10/17/02, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 8 and 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 10, filed 10/17/02.

Specification

3. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

4. The disclosure is objected to because of the following informalities: The abstract is longer than 150 words.

Appropriate correction is required.

Drawings

5. The drawings have been reviewed by an Official draftsman. A copy of the PTO 948 is attached. Correction is required.

Information Disclosure Statement

6. The IDS filed 11/27/01 has not yet been considered because the references have been separated from the application file. Upon location of the references, the IDS will be considered with the next Official action. At that time, should any art cited in the IDS be considered prior art, a new, non-final Office action will be issued.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

8. Claims 1-7, 9, 10, 12-16 and 19 are rejected under 35 U.S.C. 102(a) as being anticipated by Araki et al. (*Nucleic Acids Research*, 1998, vol. 26, no. 14, pp. 3379-3384).

Claim 1 is drawn to a purified functional polynucleotide comprising an actuator domain, a receptor domain, and a bridging domain, wherein interaction of the receptor domain with a signaling agent triggers a conformational change in the binding domain which modulates the activity of the actuator domain. Claim 2 specifies that the signaling agent is a ligand that binds to the receptor domain. Claim 3 specifies that the activity of the actuator domain is catalytic. Claim 4 specifies that the activity of the domains are non-overlapping. Claim 5 specifies that at

least two of the domains are non-overlapping. Claim 6 specifies that the polynucleotide is RNA. Claim 7 specifies that the RNA is a hammerhead ribozyme. Claim 9 specifies that the actuator domain exhibits catalytic activity that is triggered by binding of a chemical compound to the receptor domain. Claim 10 is drawn to a biosensor comprising a polynucleotide according to claim 1. Claim 11 specifies that the polynucleotide is attached to a solid support.

Claim 12 is drawn to a method for detecting the presence or absence of a ligand or its concentration in a sample comprising contacting the sample with a polynucleotide according to claim 1. Claim 13 specifies that the presence or absence of a ligand or its concentration is determined by observation of a chemical reaction. Claim 14 specifies that the presence or absence of a ligand or its concentration is detected by observation of a change in polynucleotide configuration or function.

Claim 15 is drawn to a process for preparing polynucleotides that are responsive to the presence or absence of a signaling agent, comprising linking a polynucleotide actuator domain, a receptor domain, and a bridging domain together such that interaction of the signaling agent with the receptor domain triggers a conformational change in the bridging domain which modulates the activity of the actuator domain. Claim 16 specifies wherein the receptor domain has a ligand binding site and wherein the ligand binding site triggers a conformational change in the bridging domain that stimulates catalytic activity of the actuator domain. Claim 19 is drawn to a process for preparing RNA sensors according to claim 15.

Claim 17 is drawn to a process for screening polynucleotides which have an actuator domain, a receptor domain, and a bridging domain and which are responsive to a signaling agent in a sample, comprising linking a bridging domain having defined properties that modulate the activity of a corresponding actuator domain having defined properties, to a receptor domain having a random sequence, and identifying polynucleotides responsive to the signaling agent by incubation of the sample with the polynucleotide so constructed by observation of modulation of the activity of the actuator domain. Claim 18 specifies wherein the receptor domain has a ligand binding site and wherein ligand binding triggers a conformational change in the bridging domain that stimulates catalytic activity of the actuator domain.

Araki et al. teach an allosteric ribozyme using a hammerhead ribozyme as the active site and a flavin-specific RNA aptamer as a regulatory site. They constructed six variants with a series of base pairs in the linker region (stem II). They taught that "[t]he result of chemical modification revealed that binding of FMN to the aptamer domain induced the helix formation in stem II required for catalytic activity. Therefore, a specific FMN-mediated allosteric interaction seems to promote a conformational alteration from an open to a closed structure in stem II." (See abstract and figure 1 on page 3381 for drawing of the ribozymes)

Araki et al. thus teach the compositions of claims 1-7, 9 and 10 since the ribozymes they teach in figure 1 are analogous to the allosteric ribozymes taught in the instant specification (for instance in instant figure 2A). Both the ribozymes of Araki et al. and the ribozyme in instant figure 2A modify a hammerhead ribozyme to contain an FMN aptamer domain in the stem II

area. Upon binding of the ligand chemical compound FMN to the FMN aptamer region, the ribozyme becomes catalytically active on the target nucleic acid. In a ribozyme molecule there are both domains that partially overlap (the hairpin regions) and domains that do not overlap (the regions that do not associate with other areas of the RNA) as shown in figure 1 of Araki et al.

Araki et al. further taught the methods of claims 12-16 and 19 since the methods they taught are both methods for detecting the presence or absence of a ligand or its concentration by using the FMN activated ribozymes, as well as a method for preparing polynucleotides that are responsive to the FMN ligand.

9. Claims 1-7, 9, 10, 12-16 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Tang et al. (*Chemistry and Biology*, June 1997, Vol. 4, No. 6, pp. 453-459).

See the description of the claims above.

Tang et al. taught generation of allosteric ribozymes from a hammerhead ribozyme such that the stem II region was modified to contain a region containing an ATP aptamer. The addition of ATP triggered a conformational change in the bridging domain of the ATP aptamer which increased the catalytic activity of the ribozyme. In a ribozyme molecule there are both domains that partially overlap (the hairpin regions) and domains that do not overlap (the regions that do not associate with other areas of the RNA). The methods they used for development of the allosteric ribozymes included methods of detecting the presence or absence of the ATP ligand

or its concentration in the sample and methods of preparing polynucleotides that are responsive to the presence or absence of the signaling agent, the ATP.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 11, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Araki et al., Tang et al. and Breaker (*Chem. Rev.* 1997, Vol. 97, pp. 371-390).

Araki et al. and Tang et al. are relied upon as set forth above to teach the limitations of claims 1-7, 9, 10, 12-16 and 19. They did not specifically teach the limitations of claims 11, 17

and 18: wherein the polynucleotide is attached to a solid support and wherein the receptor domain has a random sequence.

Breaker et al. is relied upon to teach that in *in vitro* evolution of ribozymes such as the allosteric ribozymes developed by Araki et al. and Tang et al., that "[a]n alternative (or complement) to rational design is the use of iterative selection methods that isolate catalytic molecules from mutagenized or random-sequence pools of RNA or DNA. This approach relies on the probability that a given pool of random-sequence molecules will include individuals that can perform the function of interest." (Page 372, col. 2) He further taught on page 373, col. 2 that one way of identifying the screened molecules is by catalytic elution to "immobilize nucleic acids on a solid support by covalent means or via the affinity of a catalyst for its substrate and then elute the active molecules by adjusting the solvent conditions to the permissive reaction conditions."

It would have been *prima facie* obvious at the time the invention was made to one of ordinary skill in the art to attach the polynucleotides taught by Araki et al. or Tang et al. to a solid support as taught by Breaker et al. for the purpose of catalytic elution of the reacted ribozyme since Breaker et al. taught that such methods of using a solid support for the isolation of the catalytic molecule was another type of selection to the gel isolation type of selection used by Araki et al. for example. It would have been *prima facie* obvious to one of ordinary skill in the art to practice a method of optimizing the allosteric ribozymes taught by Tang et al. or Araki et al. with a method of screening comprising use of randomized ribozyme sequence since Tang et

al. taught generally the use of in vitro screening techniques for optimization of the allosteric ribozymes (page 457 and page 458) in addition to the examples of rational screening, and Breaker taught that in vitro evolution experiments often use randomized sequences as an "alternative (or complement) to rational design...." (Page 372, see full quote above)

One of ordinary skill in the art would have been motivated to design allosteric ribozymes having a changed stem II region of a hammerhead ribozyme for conformational control via an FMN (Araki et al.) or ATP (Tang et al.), and further, for optimized catalytic activity of such ribozymes since Araki et al. taught motivation to design of different ribozymes for isolation of the best catalytic sequence and further, Tang et al. taught on page 458, col. 1, that "further revisions of the prototypic allosteric ribozymes described in this report could be made to refine the interplay between the aptamer and ribozyme motifs to improve the net inhibition or enhancement of ribozyme catalytic rates. These improvements can be achieved by making adjustments to the current constructs via rational design, or by constructing a combinatorial library of RNAs followed by screening via *in vitro* selection [7]." Since the reference number [7] is the Breaker (Chem. Rev. 1997, vol. 97, pp. 371-390) reference, one of skill in the art would have been motivated to rely on the teachings of Breaker in this reference to design the types of combinatorial libraries discussed therein for optimization of the allosteric ribozymes, including the use of the randomized ribozyme libraries (page 372, col. 2).

One of ordinary skill in the art would have had an expectation of success to attach the allosteric ribozymes taught by Araki et al. or Tang et al. to a solid support since the use of solid

supports in isolation of ribozymes is taught by Breaker et al. as a common step in screening methods. Furthermore, one of ordinary skill in the art would have had an expectation of success to screen for allosteric ribozymes such as those taught by Araki et al. or Tang et al. for the modification of the catalytic control of the allosteric ribozymes, since Breaker et al. taught that randomized sequences used in *in vitro* evolution experiments are useful for screening for modified ribozyme sequences.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Inquiries relating to the status of this application may also be directed to *Katrina Turner*, whose telephone number is (703) 305-3413.

M. M. Schmidt

December 28, 2002